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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ

<u>L23</u>	L22 same l21	5	<u>L23</u>
<u>L22</u>	calcium or Ca ions	539304	<u>L22</u>
<u>L21</u>	L20 with l3 with l12	28	<u>L21</u>
<u>L20</u>	vascular permeab\$	4309	<u>L20</u>
<u>L19</u>	l18 with l3 with l12	0	<u>L19</u>
<u>L18</u>	vascular pemeab\$	0	<u>L18</u>
<u>L17</u>	L16 same l5	0	<u>L17</u>
<u>L16</u>	L15 with l12	1957	<u>L16</u>
<u>L15</u>	L14 or l13	24512	<u>L15</u>
<u>L14</u>	DNA transfe?	3697	<u>L14</u>
<u>L13</u>	gene transfe\$	23037	<u>L13</u>
<u>L12</u>	enhanc\$ or increas\$	5711347	<u>L12</u>
<u>L11</u>	L10 same l5	1	<u>L11</u>
<u>L10</u>	ions	1583116	<u>L10</u>
<u>L9</u>	L8 with l5	1	<u>L9</u>
<u>L8</u>	L7 or l6	101539	<u>L8</u>

<u>L7</u>	lipid with conjugate	2939	<u>L7</u>
<u>L6</u>	PEG or conjugated lipid	99935	<u>L6</u>
<u>L5</u>	L4 with l3 with l2 with l1	1081	<u>L5</u>
<u>L4</u>	encapsula\$	202396	<u>L4</u>
<u>L3</u>	dna or nucleic or plasmid or antisense or polynucleotide	256293	<u>L3</u>
<u>L2</u>	SPLP or liposom\$ or lipid	122652	<u>L2</u>
<u>L1</u>	calcium or ca ion?	538269	<u>L1</u>

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L23: Entry 2 of 5

File: PGPB

Aug 1, 2002

DOCUMENT-IDENTIFIER: US 20020103156 A1

TITLE: Gene delivery compositions and methods

CLAIMS:

5. A method for expressing a gene product in cells of tissue of interest, comprising: treating the tissue with a vascular permeability agent under conditions of low calcium concentration to increase vascular permeability of exogenous nucleic acid; and administering exogenous nucleic acid to the tissue.

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L23: Entry 4 of 5

File: USPT

Apr 23, 2002

US-PAT-NO: 6376471

DOCUMENT-IDENTIFIER: US 6376471 B1

TITLE: Gene delivery compositions and methods

DATE-ISSUED: April 23, 2002

INVENTOR-INFORMATION:

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US-CL-CURRENT: [514/44](#); [424/93.2](#), [435/320.1](#), [435/455](#)

CLAIMS:

What is claimed is:

1. A method for delivering nucleic acid to cells in tissue of interest, comprising:

administering to the cells a permeability agent to increase vascular permeability of the cells to an exogenous nucleic acid;

administering the exogenous nucleic acid to the cells under an effective amount of low calcium ion concentrations of about 500 .mu.mol/L or less; whereby the delivery of the nucleic acid to the cells is enhanced.

2. The method of claim 1 wherein the nucleic acid is administered to the cells under calcium ion concentrations of about 40 .mu.mol/L to about 500 .mu.mol/L.

3. The method of claim 1 wherein the nucleic acid is administered by perfusion.

4. The method of claim 3 wherein a perfusate of nucleic acid is recirculated and then readministered to the cells.

5. The method of claim 1 wherein the permeability agent is serotonin, bradykinin, platelet-activating factor, prostaglandin E.sub.1, histamine, vascular endothelium growth factor, zona occludens toxin, interleukin-2, plasma kinins, L-N-monomethyl arginine or L-N-nitro-arginine methyl ester.

6. The method of claim 1 wherein the permeability agent exhibits at least about 5% of the permeability activity of bradykinin in a standard permeability assay.

7. The method of claim 1 wherein the permeability agent is perfused through

vasculature of the tissue prior to administration of the nucleic acid.

8. The method of claim 1 wherein said low calcium ion concentrations are provided by perfusing through vasculature of the tissue a fluid having a calcium ion concentration of from about 40 $\mu\text{mol/L}$ to about 500 $\mu\text{mol/L}$.

9. The method of claim 1 wherein the nucleic acid is administered to a solid cell mass.

10. The method of claim 1 wherein the nucleic acid is administered to a solid organ.

11. The method of claim 1 wherein the nucleic acid is administered to the cells of heart, lung, kidney, testes, ovaries, skeletal muscle, kidneys, brain or spleen.

12. The method of claim 1 wherein the tissue is cardiac tissue.

13. The method of claim 1 wherein the tissue is liver tissue.

14. The method of claim 1 wherein the tissue comprises malignant cells.

15. The method of claim 1 wherein the nucleic acid is administered to a solid tumor.

16. The method of claim 1 wherein the tissue is mammalian.

17. The method of claim 1 wherein the nucleic acid is administered ex vivo.

18. The method of claim 1 wherein the nucleic acid is administered in vivo.

19. The method of claim 1 wherein the nucleic acid is administered to a human.

20. The method of claim 1 wherein the nucleic acid is administered to livestock, poultry or dog or cat.

21. A method for delivering nucleic acid to malignant cells in targeted tissue, comprising:

administering to the cells a permeability agent to increase vascular permeability of the cells to an exogenous nucleic acid;

administering the exogenous nucleic acid to the cells under an effective amount of low calcium ion concentrations of about 500 $\mu\text{mol/L}$ or less; whereby the delivery of the nucleic acid to the cells is enhanced.

22. The method of claim 21 wherein the nucleic acid is administered to the cells under calcium ion concentrations of about 40 $\mu\text{mol/L}$ to about 500 $\mu\text{mol/L}$.

23. The method of claim 21 wherein the nucleic acid is administered by perfusion.

24. The method of claim 23 wherein a perfusate of nucleic acid is recirculated and then readministered to the cells.

25. The method of claim 21 wherein the permeability agent is serotonin, bradykinin, platelet-activating factor, prostaglandin E.sub.1, histamine, vascular endothelium growth factor, zona occludens toxin, interleukin-2, plasma kinins, L-N-monomethyl arginine or L-N-nitro-arginine methyl ester.

26. The method of claim 21 wherein the permeability agent exhibits at least about 5% of the permeability activity of bradykinin in a standard permeability assay.

27. The method of claim 21 wherein the permeability agent is perfused through vasculature of the tissue prior to administration of the nucleic acid.

28. The method of claim 21 wherein a fluid is perfused through vasculature of the tissue by a fluid having a calcium ion concentration of from about 40 .mu.mol/L to about 500 .mu.mol/L.

29. The method of claim 21 wherein said targeted tissue comprises a solid tumor comprising the malignant cells.

30. The method of claim 21 wherein the malignant cells are present in a lung, liver, prostate, brain, testes or ovaries of a subject.

31. The method of claim 21 wherein the nucleic acid is administered to a human.

32. A method for delivering nucleic acid to cells in tissue of interest, comprising:

administering to the cells i) a permeability agent to increase vascular permeability of the cells to an exogenous nucleic acid, and ii) the exogenous nucleic acid under an effective amount of low calcium ion concentrations of about 500 .mu.mol/L or less, whereby the delivery of the nucleic acid to the cells is enhanced.

33. The method of claim 32 wherein the nucleic acid is administered to the cells under calcium ion concentrations of about 40 .mu.mol/L to about 500 .mu.mol/L.

34. The method of claim 32 wherein the nucleic acid is administered by perfusion.

35. The method of claim 34 wherein the perfusate of nucleic acid is recirculated and then readministered to the cells.

36. The method of claim 32 wherein the permeability agent is serotonin, bradykinin, platelet-activating factor, prostaglandin E.sub.1, histamine, vascular endothelium growth factor, zona occludens toxin, interleukin-2, plasma kinins, L-N-monomethyl arginine or L-N-nitro-arginine methyl ester.

37. The method of claim 32 wherein the permeability agent exhibits at least about 5% of the permeability activity of bradykinin in a standard permeability assay.

38. The method of claim 32 wherein the permeability agent is perfused through vasculature of the tissue prior to administration of the nucleic acid.

39. The method of claim 32 wherein low calcium ion concentration conditions are provided by perfusing through vasculature of the tissue a fluid having a calcium ion concentration of from about 40 $\mu\text{mol/L}$ to about 500 $\mu\text{mol/L}$.

40. A nucleic acid enhanced delivery kit comprising:

a permeability agent that increases vascular permeability of a subject; a nucleic acid for administration to a subject; and a solution having an effective amount of a calcium ion concentration that enhances the delivery of the nucleic acid to the subject, wherein said concentration is about 500 $\mu\text{mol/L}$ or less.

41. The kit of claim 40 further comprising a device for delivery of the nucleic acid.

42. The kit of claim 40 wherein the delivery device is a catheter.

43. The kit of claim 40 wherein the nucleic acid is present in the kit as a viral vector.

44. The kit of claim 40 wherein the solution has a calcium ion concentration of about 40 $\mu\text{mol/L}$ to about 500 $\mu\text{mol/L}$.

45. A treatment solution comprising:

a permeability agent that increases vascular permeability of cells to an exogenous nucleic acid; a nucleic acid; and a solution having an effective amount of a calcium ion concentration that enhances the delivery of the nucleic acid to the cells, wherein said concentration is about 500 $\mu\text{mol/L}$ or less.

46. The solution of claim 45 wherein the solution is pharmaceutically acceptable.

47. The solution of claim 45 wherein the solution comprises one or more therapeutic agents in addition to the nucleic acid.

48. The solution of claim 45 wherein the solution comprises one or more vascular permeability agents.

49. The solution of claim 45 wherein the permeability agent is serotonin, bradykinin, platelet-activating factor, prostaglandin E.sub.1, histamine, vascular endothelium growth factor, zona occludens toxin, interleukin-2, plasma kinins, L-N-monomethyl arginine or L-N-nitro-arginine methyl ester.

50. The solution of claim 45 wherein the solution has a calcium ion concentration of about 40 $\mu\text{mol/L}$ to about 500 $\mu\text{mol/L}$.

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